



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 49/04		A1	(11) International Publication Number: WO 95/28969
			(43) International Publication Date: 2 November 1995 (02.11.95)
(21) International Application Number: PCT/GB95/00566		(72) Inventors: RUDDY, Stephen, B.; 226 Stallion Lane, Schwenksville, PA 19473 (US). MCINTIRE, Gregory, L.; 113 Piedmont Road, Westchester, PA 19382 (US). ROBERTS, Mary, E.; 1358 Westminster Drive, Downingtown, PA 19355 (US). TONER, John; 109 Brookhollow Drive, Downingtown, PA 19355 (US). BACON, Edward, R.; 1006 Skyline Circle, Audubon, PA 19403 (US). CAULFIELD, Tom; 2951 Appledale Road, Audubon, PA 19403 (US). COOPER, Eugene, R.; 2621 Crum Creek Drive, Berwyn, PA 19312 (US). DOUTY, Brent, D.; Box 475B, Strasburg Road, Coatsville, PA 19320 (US). ILLIG, Carl, R.; 25 Jonathan Drive, Phoenixville, PA 19460 (US). ESTEP, Kimberly; 420 Ellis Woods Road, Pottstown, PA 19464 (US).	
(22) International Filing Date: 16 March 1995 (16.03.95)			
(30) Priority Data:			
230,580	21 April 1994 (21.04.94)	US	
236,287	29 April 1994 (29.04.94)	US	
237,502	3 May 1994 (03.05.94)	US	
239,090	5 May 1994 (05.05.94)	US	
247,438	23 May 1994 (23.05.94)	US	
247,424	23 May 1994 (23.05.94)	US	
249,424	26 May 1994 (26.05.94)	US	
(71) Applicant: NYCOMED IMAGING AS [NO/NO]; Nycoveien 1-2, N-0401 Oslo (NO).		(74) Agent: FRANK B. DEHN & CO.; Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).	
(71) Applicant (for GB only): MATTHEWS, Derek, Peter [GB/GB]; 15-19 Kingsway, London WC2B 6UZ (GB).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).	
		Published <i>With international search report.</i>	
(54) Title: X-RAY CONTRAST COMPOSITIONS CONTAINING PHARMACEUTICALLY ACCEPTABLE CLAYS			
(57) Abstract			
<p>Disclosed are x-ray contrast compositions for oral or retrograde examination of the gastrointestinal tract comprising an x-ray contrast producing agent in combination with a pharmaceutically acceptable clay in a pharmaceutically acceptable carrier; and methods for their use in diagnostic radiology of the gastrointestinal tract.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

- 1 -

X-RAY CONTRAST COMPOSITIONS CONTAINING
PHARMACEUTICALLY ACCEPTABLE CLAYS

This invention relates to an x-ray contrast composition for oral or retrograde administration to a mammal comprising an x-ray contrast producing agent and a pharmaceutically acceptable clay.

Roentgenographic examination utilizing x-rays and computed tomography (hereinafter CT) scans of fractures and other conditions associated with the skeletal system is routinely practiced without the use of contrast agents. X-ray visualization of organs containing soft tissue, such as the gastrointestinal (hereinafter GI) tract, requires the use of contrast agents which attenuate x-ray radiation. D. P. Swanson et al in "Pharmaceuticals In Medical Imaging", 1990, MacMillan Publishing Company, provide an excellent background in medical imaging utilizing contrast agents.

Roentgenographic examination of the GI tract is indicated for conditions of digestive disorders, changes in bowel habit, abdominal pain, GI bleeding and the like. Prior to radiological examination, administration of a radiopaque contrast medium is necessary to permit adequate delineation of the respective lumen or mucosal surface from surrounding soft tissues. Accordingly, a contrast medium is administered orally to visualize the mouth, pharynx, esophagus, stomach, duodenum and proximal small intestine. The contrast medium is administered rectally for examination of the distal small intestine and the colon.

The most widely used contrast agent for the visualization of the GI tract is barium sulfate administered orally as a suspension or rectally as an enema. (See, for example, U.S. Patent Nos.: 2,659,690;

- 2 -

2,680,089; 3,216,900; 3,235,462; 4,038,379 and 4,120,946) Notwithstanding its relatively good contrast characteristics, negligible absorption from the GI tract following oral or rectal administration and speedy excretion from the body, barium sulfate has certain disadvantages. In the presence of intestinal fluids it lacks homogeneity and poorly adheres to mucus membranes which can result in poor x-ray images. In the colon, when administered as an enema, it flocculates and forms irregular clumps with fecal matter.

Iodinated organic compounds have also been used as contrast agents since the iodine atom is an effective x-ray absorber. They have the most versatility and are utilized in the widest variety of procedures. They are very absorptive of x-rays, with which the iodine interacts and produces a so-called photoelectric effect which is a large magnification in contrast caused by the photons stopped in the iodine-containing medium. The magnification of contrast exceeds the level that would be expected from relative changes in density. Because of this magnification, relatively low concentrations of the contrast agent can be utilized. (For iodinated agents see, for example, U.S. Patent Nos.: 2,786,055; 3,795,698; 3,360,436; 3,574,718, 3,733,397; 4,735,795 and 5,047,228.)

The desiderata for an ideal GI contrast agent include: good toxicological profile; the ability to fill the entire bowel/lumen and evenly coat the gut mucosa so that the presence of the bowel is detectable when the lumen is not distended; palatability and nonirritation to the intestinal mucosa; and passing through the GI tract without producing artifacts or stimulating vigorous intestinal peristalsis.

These requirements were addressed by many investigators and their efforts resulted in great improvements over the years. The requirement of evenly coating the gut mucosa with, and sufficiently adhering

- 3 -

thereto, a contrast agent to effectively cover the walls of the intestines proved to be rather difficult. Without meeting these requirements it is impossible to obtain x-ray pictures of high precision. To that end, the use of certain polymer additives were proposed as illustrated hereunder.

U.S. Patent No. 4,069,306 discloses an x-ray contrast preparation which is said to adhere to the walls of body cavities. The preparation comprises a finely divided water-insoluble inorganic x-ray contrast agent and minute particles of a hydrophilic polymer which is insoluble in water but is water-swellable. The body cavity is supplied with such preparation suspended in water. The x-ray contrast agent is present in admixture with and/or enclosed in and/or adhered to said minute polymer particles.

U.S. Patent No. 4,120,946 discloses a pharmaceutical composition for barium opacification of the digestive tract, comprising colloidal barium sulfate and a polyacrylamide in an aqueous vehicle. The polyacrylamide forms a viscous solution at low concentration which makes it possible to maintain the barium sulfate in suspension and at the same time permit good adherence of the preparation to the walls of the organ which it is desired to x-ray.

U.S. Patent No. 5,019,370 discloses a biodegradable radiographic contrast medium comprising biodegradable polymeric spheres which carry a radiographically opaque element, such as iodine, bromine, samarium and erbium. The contrast medium is provided either in a dry or liquid state and may be administered intravenously, orally and intra-arterially.

While these polymeric materials greatly enhance attachment of the contrast agent used therewith to the walls of organs for better visualization thereof, there is still a need for an improved x-ray imaging medium that uniformly coats the soft tissues subjected to

- 4 -

diagnostic x-ray examination.

We have now discovered that the use of certain natural clays in combination with an x-ray producing agent enhances the uniformity of coating on the gastrointestinal tract and the quality of x-ray images. In addition, these clays mask the unpleasant odor and taste of the x-ray contrast formulations as well as enhance the physical stability thereof.

It is the object of the present invention to provide compositions for coating the gastrointestinal tract of mammals to form an effective radiopaque coating thereon by which diagnostic examination of the GI tract may be accomplished. To that end, a thin coating is formed on the inner surface of the GI tract effected by ingesting, prior to visualization by an x-ray emitting device, a composition containing a pharmaceutically acceptable clay and an x-ray contrast agent. Such compositions must meet several requirements: both the x-ray contrast agent and the clay must be nontoxic; must not contain leachable or digestible components that would deleteriously affect the patient; and no components of the coating should be absorbed by, and pass through, the inner surface of the intestine.

The object of the present invention is achieved by a composition comprising: an x-ray contrast agent and a pharmaceutically acceptable clay in an aqueous pharmaceutically acceptable vehicle.

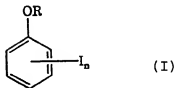
In accordance with the invention there is further provided a method for x-ray diagnostic imaging of the GI tract which comprises orally or rectally administering to the patient an effective contrast producing amount of the above-described x-ray contrast composition.

The contrast agent and the pharmaceutically acceptable clay are incorporated in liquid media for administration to a mammal for x-ray visualization of the GI tract.

- 5 -

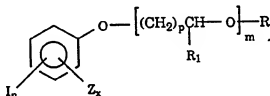
The contrast agents utilized in the present invention are selected from

- (1) compounds of the formula (I)




wherein R is a substituted or unsubstituted alkyl group containing from 2 to 8 carbon atoms, wherein said substituents are selected from the group consisting of C₁-C₆ alkyl, hydroxy and alkoxy; and n is 1 to 5;

- (2) a compound of the formula



or a pharmaceutically acceptable salt thereof wherein

Z is H, halo, C₁-C₂₀ alkyl, cycloalkyl, lower alkoxy, alkoxy-carbonyl, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C₁-C₂₅ alkyl, cycloalkyl,  or halo-lower-alkyl, each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy; or (CR₁R₂)_p-(CR₃=CR₄)_mQ, or (CR₁R₂)_p-C≡C-Q;

R₁, R₂, R₃ and R₄ are independently H or lower-alkyl, optionally substituted with halo;

x is 1-4;

n is 1-4;

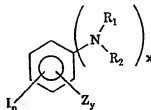
m is 1-15;

p is 1-20; and

- 6 -

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower alkyl;

(3) a compound of the formula



or a pharmaceutically acceptable salt thereof wherein

Z is H, halo, C₁-C₂₀ alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

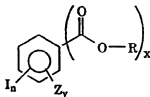
R₁ and R₂ are independently H, C₁-C₂₅ alkyl, cycloalkyl, acetyl or halo-lower-alkyl, wherein said C₁-C₂₅ alkyl, cycloalkyl and halo lower-alkyl are optionally substituted with fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy and said acetyl is optionally substituted with fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy;

n is 1-4;

y is 1-4; and

x is 1 or 2;

(4) a compound of the formula



wherein

Z is H, halo, C₁-C₂₀ alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C₁-C₂₅ alkyl, cycloalkyl, or halo-lower-alkyl,

- 7 -

each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy; or $(CR_1R_2)_p-(CR_3=CR_4)_mQ$, or $(CR_1R_2)_p-C\equiv C-Q$;

R_1 , R_2 , R_3 and R_4 are independently lower-alkyl, optionally substituted with halo;

x is 1-3

y is 1-4;

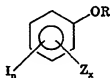
n is 1-5;

m is 1-15;

p is 1-10; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower alkyl;

(5) a compound of the formula



or a pharmaceutically acceptable salt thereof wherein

Z is H, halo, C_1 - C_{20} alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is methyl, ethyl, propyl, C_3 - C_{25} alkyl, cycloalkyl, or halo-lower-alkyl, optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy; or $(CR_1R_2)_p-(CR_3=CR_4)_mQ$, or $(CR_1R_2)_p-C\equiv C-Q$;

R_1 , R_2 , R_3 and R_4 are independently lower-alkyl, optionally substituted with halo;

x is 1-4;

n is 1-5;

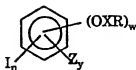
m is 1-15;

p is 1-10; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower alkyl;

- 8 -

(6) a compound of the formula



wherein

X is $\begin{array}{c} \text{O} \\ | \\ -\text{C}- \end{array}$ or $-\text{SO}_2-$;

Z is H, halo, methyl, ethyl, n-propyl, C_4 - C_{20} alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C_1 - C_{25} alkyl, cycloalkyl or aryl each of which may be optionally substituted with halo, fluoro-lower-alkyl, lower-alkoxy, hydroxy, carboxy or lower-alkoxy carbonyl; lower-alkenyl, lower-alkynyl, lower-alkylene or lower-alkoxy-carbonyloxy;

n is 1-5;

y is 0-4; and

w is 1-4;

(7) a particulate crystalline x-ray contrast agent having a surface modifier adsorbed on the surface thereof.

As used herein, the term halogen (or halo) means fluorine, chlorine, bromine or iodine.

As used herein, the term cycloalkyl means carbocyclic rings having from three to eight ring carbon atoms including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cyclooctyl which may be substituted on any ring carbon atom thereof by one or more lower-alkyl groups, lower-alkoxy groups or halogens.

As used herein the terms lower-alkyl and lower-alkoxy mean monovalent aliphatic radicals, including

- 9 -

branched chain radicals, of from one to ten carbon atoms. Thus, the lower-alkyl moiety of such groups include, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, t-butyl, n-pentyl, 2-methyl-3-butyl, 1-methylbutyl, 2-methylbutyl, neopentyl, n-hexyl, 1-methylpentyl, 3-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 2-hexyl, 3-hexyl, 1,1,3,3-tetramethylpentyl, 1,1-dimethyloctyl and the like.

As used herein, the terms lower-alkenyl and lower-alkynyl means monovalent, unsaturated radicals including branched chain radicals of from three to ten carbon atoms and thus include 1-ethenyl, 1-(2-propenyl), 1-(2-butenyl), 1-(1-methyl-2-propenyl), 1-(4-methyl-2-pentenyl), 4,4,6-trimethyl-2-heptenyl, 1-ethynyl, 1-(2-propynyl), 1-(2-butylnyl), 1-(1-methyl-2-propynyl), 1-(4-methyl-2-pentynyl) and the like.

As used herein, the term alkylene means divalent saturated radicals, including branched chain radicals of from two to ten carbon atoms having their free valences on different carbon atoms and thus includes 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1-methyl-1,2-ethylene, 1,8-octylene and the like.

As used herein, the term aryl means an aromatic hydrocarbon radical having six to ten carbon atoms. The preferred aryl groups are phenyl, substituted phenyl and naphthyl substituted by from one to three, the same or different members of the group consisting of lower-alkyl, halogen, hydroxy-lower-alkyl, alkoxy-lower-alkyl and hydroxy.

The x-ray contrast compounds can comprise one, two, three or more iodine atoms per molecule; preferred species contain at least two, and more preferably, at least three iodine atoms per molecule.

Solid x-ray contrast agents in particulate forms useful in the practice of the present invention can be prepared by techniques known in the art. The solid agents are comminuted to the desired size using

- 10 -

conventional milling methods, such as airjet or fragmentation milling. We have found that an effective average particle size of less than about 100μ provides for good distribution and coating in the GI tract. As used herein, particle size refers to a number average particle size as measured by conventional techniques, such as sedimentation field flow fractionation and disk centrifugation. An effective average particle size of less than about 100μ means that at least about 90% of the particles have a weight average particle size of less than about 100μ as measured by art recognized techniques.

The compositions may be in the form of dispersions, suspensions when the x-ray contrast agent is a solid, or emulsions when the x-ray contrast agent is an oil; we prefer to use emulsions as the preferred embodiment.

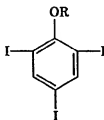
The natural clays incorporated in the compositions of the present invention are selected from the group consisting of montmorillonite, beidelite, nontronite, hectorite and saponite.

A method for diagnostic imaging of the GI tract for use in medical procedures in accordance with this invention comprises orally or rectally administering to the mammalian patient in need of an x-ray examination, an effective contrast producing amount of a composition of the present invention. After administration at least a portion of the GI tract containing the administered composition is exposed to x-rays to produce an x-ray image pattern corresponding to the presence of the contrast agent, then the x-ray image is visualized and interpreted using techniques known in the art.

Compounds of type (1) defined above are described in EP-A-568155. For example, 2,4,6-triiodophenoxy-2-octane, 2,4,6-triiodophenoxy-2-butane, 2,4,6-triiodophenoxy-2-hexane and 4-iodophenoxy-2-octane are described therein.

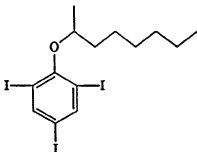
- 11 -

Preferred contrast agents of type (1) have the formula:



wherein R is a secondary alkyl group containing from 4 to 8 carbon atoms.

The most preferred contrast agent of type (1) is the sec-octyl ether of 2,4,6-triiodophenol having the formula:



Compounds of type (2) defined above are described in EP-A-614670. For example, the bis-(4-iodophenyl) ether of polyethylene-glycol-400, 1,8-bis-O-(2,4,6-triiodophenyl)-tripropylene glycol, 1,11-bis-(2,4,6-triiodophenoxy)-3,6,9-trioxaundecane, 1,2-bis-(2,4,6-triiodophenoxy)-ethane, the bis-O-(2,4,6-triiodophenyl) ether of polyethylene glycol 400, 1-(3-iodophenoxy)-3,6,9-trioxadecane, 1,3-bis-(2,4,6-triiodophenoxy)-butane, 1-(3-iodophenoxy)-6-(2,4,6-triiodophenoxy)-hexane and 1,12-bis-(2,4,6-triiodophenoxy)-dodecane are described therein.

Compounds of type (3) as defined above are described in EP-A-613689. For example, N-acetyl-N-2-octyl-4-iodoaniline and N-(4'-iodophenyl)-2-aminoctane are described therein.

- 12 -

Compounds of type (4) as defined above are described in EP-A-614669. For example, 2-octyl 2,3,5-triiodobenzoate, 3,3,4,4,5,5,6,6,7,7,8,8-dodecafluoro-2-octyl 2,3,5-triiodobenzoate, bis (2-hexyl) 2,3,5,6-tetraiodoterephthalate, ethyl 3-(2-octyloxy)-2,4,6-triiodobenzoate and bis(2-octyl) 5-(2-octyloxy)-2,4,6-triiodoisophthalate are described therein.

Compounds of type (5) as defined above are described in EP-A-609587. For example, 2-(4-iodophenoxy)-decane, 2-(2,4,6-triiodophenoxy)-pentadecane, 2-(2,4,6-triiodophenoxy)decane, (2,4,6-triiodophenoxy)-1H,1H,2H,2H-perfluorooctane, 1-(2,4,6-triiodo-3-trifluorophenoxy)octane, 2-(2,4,6-triiodophenoxy)-nonane, 2-ethyl-1-(2,4,6-triiodophenoxy)-hexane, 3,3-diphenyl-1-(2,4,6-triiodophenoxy)propane, 3-(2,4,6-triiodophenoxy)-nonane, 2-(4-iodophenoxy)-undecane, 2-iodophenoxy-cyclopentane, 3-iodophenoxy-cyclopentane, (3,5-dimethyl-2,4,6-triiodophenoxy)cyclopentane, 2-(4-iodophenoxy)-pentadecane, 4-iodophenoxy-cyclopentane, 2,4,6-triiodophenoxy-cyclopentane, 2,4,6-triiodophenoxy-methylcyclopentane, 2-(2,4,6-triiodophenoxy)ethylcyclopentane, (E,E)-1-(2,4,6-triiodophenoxy)-3,7,11-trimethyl-2,6,10-dodecatriene, 1-(2,4,6-triiodophenoxy)-3,7-dimethyl-6-octene, (E)-1-(3,5-dimethyl-2,4,6-triiodophenoxy)-3,7-dimethyl-2,6-octadiene, (E)-1-(2,4,6-triiodophenoxy)-3,7-dimethyl-2,6-octadiene, 1-(2,4,6-triiodophenoxy)-3-octyne, 2-(2,4,6-triiodophenoxy)-4-octyne, 1-(2,4,6-triiodophenoxy)-3-octyne, diethyl 2-(2,4,6-triiodophenoxy)-1,3-propanedioate, diisopropyl 2-(2,4,6-triiodophenoxy)-1,3-propanedioate, ethyl 2,2-bis-(3-iodophenoxy)acetate, ethyl 5-(2,4,6-triiodophenoxy)hexanoate, 5-(2,4,6-triiodophenoxy)-hexan-1-ol, 10-(4-iodophenoxy)-undecan-1-ol, ethyl 5-(2,4,6-triiodophenoxy) hexyl carbonate and ethyl 10-(3-

- 13 -

iodophenoxy)-undecanoate are described therein.

Compounds of type (6) as defined above are described in EP-617970. For example, 2,4,6-triiodophenyl 2-ethylhexanoate, 2,4,6-triiodophenyl 2-methylpentanoate, 2,4,6-triiodophenyl 3-cyclopentyl propionate, 2,4,6-triiodophenyl (2-propyl)pentanoate, 2,4,6-triiodophenyl perfluoroheptanoate, 2,4,6-triiodophenyl-tris-(2-ethyl)-hexanoate, 2,4,6-triiodophenyl dodecanoate, 3-trifluoromethyl-2,4,6-triiodophenyl 2-ethyl hexanoate, 2,4,6-triiodophenyl-bis-(2-methylpentanoate), 2,4,6-triiodophenyl hexanesulfonate, 2,4,6-triiodophenyl heptanesulfonate and 2,4,6-triiodophenyl decanesulfonate are described therein.

Compounds used in the compositions of type (7) defined above are non-radioactive and exist as a discrete, crystalline phase of an organic substance. The crystalline phase differs from an amorphous or non-crystalline phase which results from solvent precipitation techniques such as described in U.S. Patent 4,826,689 noted above. The organic substance can be present in one or more suitable crystalline phases. The invention can be practiced with a wide variety of crystalline, non-radioactive x-ray contrast agents. However, the x-ray contrast agent must be poorly soluble and dispersible in at least one liquid medium. By "poorly soluble", it is meant that the agent has a solubility in the liquid dispersion medium, e.g., water, of less than about 10 mg/ml, and preferably of less than about 1 mg/ml. The preferred liquid dispersion medium is water. Additionally, the invention can be practiced with other liquid media in which the selected x-ray contrast agent is poorly soluble and dispersible, including, for example, aqueous saline solutions, such as phosphate buffered saline (PBS), plasma, mixed

- 14 -

aqueous and nonaqueous solutions, for example, water and alcohol, and suitable nonaqueous solvents such as alcohol, glycerol and the like.

The x-ray contrast agent can be an iodinated compound. The iodinated compound can be aromatic or nonaromatic. Aromatic compounds are preferred. The iodinated compound can comprise, one, two, three or more iodine atoms per molecule. Preferred species contain at least two, and more preferably, at least three iodine atoms per molecule. The iodinated compounds selected can contain substituents that do not impart solubility to the compound, such as, for example, alkylureido, alkoxyacylamido, hydroxyacetamido, butyrolactamido, succinimido, trifluoroacetamido, carboxy, carboxamido, hydroxy, alkoxy, acylamino, and the like substituents.

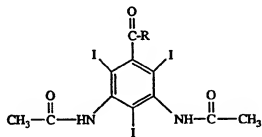
A preferred class of contrast agents includes various esters and amides of iodinated aromatic acids. The esters preferably are alkyl or substituted alkyl esters. The amides can be primary or secondary amides, preferably alkyl or substituted alkyl amides. For example, the contrast agent can be an ester or amide of a substituted triiodobenzoic acid such as an acyl, carbamyl, and/or acylmethyl substituted triiodobenzoic acid. Illustrative representative examples of iodinated aromatic acids include, but are not limited to, diatrizoic acid, metrizoic acid, iothalamic acid, trimesic acid, urokonic acid, ioxaglic acid (hexabrix), ioxitalamic acid, tetraiodoterephthalic acid, iodipamide, icarmic acid, and the like.

Many of the iodinated molecules described above, if in monomeric form, can also be prepared as dimers (sometimes referred to as bis compounds), trimers (sometimes referred to as tris compounds), etc., by techniques known in the art. It is contemplated that this invention can be practiced with poorly soluble-iodinated compounds in monomeric, dimeric, trimeric and polymeric forms.

- 15 -

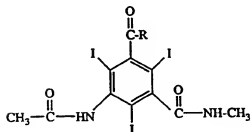
Classes of preferred contrast agents have the following structural formulae:

A.



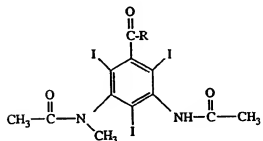
[diatrizoate]

B.

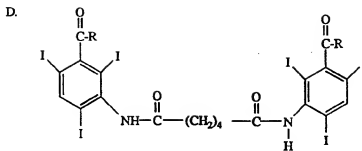


[iothalamate]

C.



- 16 -



[iodipamide]

In the above structures R can be OR^1 , NR^2R^3 , alkylene, $-CO.OR^1$ or $-O$ -alkylene- $CO.OR^1$ wherein R^1 is alkyl, and R^2 and R^3 are independently H or alkyl.

Each alkyl group can independently contain from 1-20, preferably 1-8, and more preferably, 1-4 carbon atoms.

The alkylene group preferably contains from 1 to 4 carbon atoms such as methylene, ethylene, propylene and the like.

Particularly preferred contrast agents include the ethyl ester of diatrizoic acid, i.e., ethyl 3,5-diacetamido-2,4,6-triiodobenzoate, also known as ethyl 3,5-bis(acetylamino)-2,4,6-triiodobenzoate or ethyl diatrizoate, having the structural formula A above wherein $R = -OCH_2CH_3$; the ethyl glycolate ester of diatrizoic acid, i.e., ethyl (3,5-bis(acetylamino)-2,4,6-triiodobenzoyloxy)acetate, also known as ethyl diatrizoxyacetate; and ethyl 2-(3,5-bis(acetylamino)-2,4,6-tri-iodobenzoyloxy)butyrate, also known as ethyl 2-diatrizoxybutyrate.

In addition, the invention can be practiced in conjunction with the water insoluble iodinated carbonate esters described in PCT/EP90/00053.

The above described x-ray contrast agents are known compounds and/or can be prepared by techniques known in the art. For example, water-insoluble esters and

- 17 -

terminal amides of acids such as the above-described iodinated aromatic acids can be prepared by conventional alkylation or amidation techniques known in the art. The above-noted acids and other acids which can be used as starting materials are commercially available and/or can be prepared by techniques known in the art.

The particles useful in the contrast agents of type (7) include a surface modifier. Surface modifiers useful herein physically adhere to the surface of the x-ray contrast agent but do not chemically react with the agent or itself. Individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages. Suitable surface modifiers can be selected from known organic and inorganic pharmaceutical excipients such as various polymers, low-molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of surface modifiers include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available Tweens, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone (PVP). Most of these surface modifiers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the

- 18 -

American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986, the disclosure of which is hereby incorporated by reference in its entirety.

Particularly preferred surface modifiers include polyvinylpyrrolidone, tyloxapol, poloxamers such as Pluronic F68 and F108, which are block copolymers of ethylene oxide and propylene oxide, and poloxamines such as Tetronic 908 (also known as Poloxamine 908), which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine, available from BASF, dextran, lecithin, dialkylesters of sodium sulfosuccinic acid, such as Aerosol OT, which is a dioctyl ester of sodium sulfosuccinic acid, available from American Cyanamid, Duponol P, which is a sodium lauryl sulfate, available from DuPont, Triton X-200, which is an alkyl aryl polyether sulfonate, available from Rohm and Haas, Tween 80, which is a polyoxyethylene sorbitan fatty acid ester, available from ICI Specialty Chemicals, and Carbowax 3350 and 934, which are polyethylene glycols available from Union Carbide. Surface modifiers which have been found to be particularly useful include Tetronic 908, the Tweens, Pluronic F-68 and polyvinylpyrrolidone.

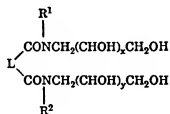
Other useful surface modifiers include:

decanoyl-N-methylglucamide;
n-decyl β -D-glucopyranoside;
n-decyl β -D-maltopyranoside;
n-dodecyl β -D-glucopyranoside;
n-dodecyl β -D-maltoside;
heptanoyl-N-methylglucamide
n-heptyl β -D-glucopyranoside;
n-heptyl β -D-thiogluconide;
n-hexyl β -D-glucopyranoside;
nonanoyl-N-methylglucamide;

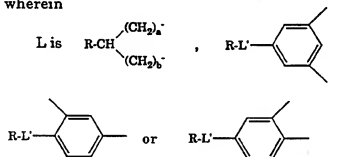
- 19 -

n-nonyl β -D-glucopyranoside;
 octanoyl-N-methylglucamide;
 n-octyl β -D-glucopyranoside;
 octyl β -D-thiogluconopyranoside;
 and the like.

A particularly preferred class of surface modifiers includes water-soluble or water-dispersible compounds having the formula



wherein



L' is a chemical bond, -O-, -S-, -NH-, -CONH- or -SO₂NH-;

R is a hydrophobic substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted aryl group;

each of R¹ and R² independently is hydrogen or an alkyl group having from 1 to 4 carbon atoms;

each of a and b independently is 0 or an integer from 1 to 3, provided that the sum of a and b is not greater than 3; and,

- 20 -

each of x and y independently is an integer from 3 to 7.

Preferred compounds within this class conform to the above structure wherein R contains from 6 to 36 carbon atoms, for example, R is an n-alkyl group containing from 6 to 18 carbon atoms, each of R¹ and R² independently is a methyl, ethyl, propyl or butyl group and a is 0 and b is 0. This class of surface modifiers is described in U.K. Patent Application No. 9104957.7 filed March 8, 1991 and can be prepared by reacting an appropriate dicarboxylic acid ester with an appropriate monosaccharide amine, preferably in the absence of a solvent, at a reaction temperature from 140 to 200°C.

The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

The particles can be prepared in accordance with the wet grinding process described in U.S. Patent No. 5,145,684. The process comprises dispersing a poorly soluble x-ray contrast agent in a liquid dispersion medium and wet-grinding the agent in the presence of grinding media to reduce the particle size of the contrast agent to an effective average particle size of from about 0.05 μ to about 100 μ , preferably of from about 0.05 μ to about 5 μ and most preferably from about 0.1 μ to about 1 μ . The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

As used herein, particle size refers to a number average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk centrifugation. By "an effective average particle size

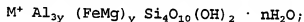
- 21 -

of from about 0.05μ to about 100μ " is meant that at least 90% of the particles have a weight average particle size of from about 0.05μ to about 100μ when measured by the above-noted techniques. The particle size range allows sufficient number of particles' distribution in the film forming composition when the GI tract is coated therewith, yet insures against absorption through the intestinal walls.

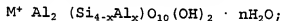
The natural, pharmaceutically acceptable clays incorporated in the present invention comprise aluminum silicates. They are used in purified form, suitable for administration to patients. The natural, pharmaceutically acceptable clays of the present invention, generally referred to as smectites, consist of dioctahedral smectites and trioctahedral smectites.

Dioctahedral smectites include:

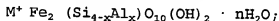
montmorillonite, having the formula



beidelite, having the formula



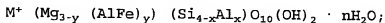
nontronite, having the formula



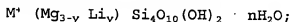
wherein M^+ is Na, Ca or Mg.

Trioctahedral smectites include:

saponite, having the formula



hectorite, having the formula



- 22 -

wherein M* is Na, Ca or Mg.

The clays are available from chemical suppliers, such as, for example, American Colloid Company, Arlington Heights, IL, under the tradenames:

MAGNABRITE®HS;
HECTABRITE®DP,
HECTABRITE®LT,
CARMARGO®White,
POLARGEL®NF,
POLARGEL®HV, and
VOLCLAY®NF-BC.

Other suppliers include: Engelhard Corp., Iselin, NJ; Ashland Chemical Inc., Columbus, OH; RT Vanderbilt Co., Inc., Norwalk, CT and Whittaker Clark & Daniels, Inc., S. Plainfield, NJ.

The contrast agent and the pharmaceutically acceptable clay are formulated for administration using physiologically acceptable carriers or excipients in a manner within the skill of the art. The contrast agent with the addition of pharmaceutically acceptable aids (such as surfactants and emulsifiers) and excipients may be suspended or emulsified in an aqueous medium resulting in a suspension or emulsion.

Compositions of the present invention comprise the following pharmaceutically acceptable components based on % w/v:

- 23 -

<u>Ingredients</u>	<u>Broad Range</u>	<u>Preferred Range</u>	<u>Most</u>
			<u>Preferred Range</u>
Contrast agent	5 - 45	10 - 35	15 - 25
Clay	0.1 - 10	0.5 - 5	1 - 2
Surfactant	1 - 20	2 - 10	3 - 5
Excipients	0 - 15	0.5 - 5	1 - 2

Water - q.s. to 100% by volume

Excipients contemplated by the present invention include antifoaming agents, such as simethicone, siloxyalkylene polymers and polyoxyalkylated natural oils; preservatives, such as methyl paraben, propyl paraben, benzoic acid and sorbic acid; flavoring/sweetening agents, such as sodium saccharine; and coloring agents, such as lakes and dyes.

While the iodophenoxyalkanes of the present invention in formulations with a pharmaceutically acceptable vehicle provide good quality x-ray images, the addition of a pharmaceutically acceptable clay to the formulations greatly increases the quality of the x-ray images. At the low extreme of the concentration range there is little or no benefit gained, while above the higher extreme of the concentration range the formulation is too viscous for administration.

The following formulation examples will further illustrate the invention.

Example 1

Components

2,4,6-triiodophenoxy-2-butane	20.0 g
HECTABRITE® DP	1.45 g
Sorbitan monostearate	0.5 g
Polysorbate 60	1.0 g
Poloxamer 338	5.0 g

- 24 -

Sodium Saccharine	0.25 g
Benzoic acid	0.50 g
Sorbic Acid	0.050 g
Water q.s. to make 100 ml	

Example 2Components

4-Iodophenoxy-2-octane	22.5 g
POLARGEL® NF	2.25 g
Sorbitan mono-oleate	0.40 g
Polysorbate 20	1.25 g
Polyvinyl alcohol	4.50 g
Sodium Saccharine	0.25 g
Simethicone emulsion (food-grade)	0.10 g
Water q.s. to make 100 ml	

Example 3Components

2,4,6-triiodophenoxy-2-hexane	18.5 g
MAGNABRITE® HS	1.25 g
Sorbitan monopalmitate	0.6 g
Polyoxyethylene myristyl ether	0.6 g
Polyvinylpyrrolidone	3.5 g
Vanilla flavoring (artificial)	0.25 g
Strawberry flavoring (artificial)	0.25 g
Sorbitol	1.0 g
Water q.s. to make 100 ml	

Example 4ComponentsAmounts in % w/v

Bis-(4-iodophenyl) ether of polyethylene glycol-400	17.50
HECTABRITE® DP	1.35
Polysorbate 80 (Tween 80)	1.50

- 25 -

Sorbitan Mono-oleate (Span 80) 1.65
 q.s. with water to 100% by volume

Example 5

<u>Components</u>	<u>Amounts in % w/v</u>
1,8-Bis-O-(2,4,6-triiodophenyl)- tripropylene glycol	25.00
POLARGEL®NF	2.30
Polysorbate 60 (Tween 60)	1.00
Poloxamer 338	6.50
Benzoic Acid	0.50
Sorbic Acid	0.05
q.s. with water to 100% by volume	

Example 6

<u>Components</u>	<u>Amounts in % w/v</u>
1,11-Bis-(2,4,6-triiodophenoxy)- 3,6,9-trioxaundecane	17.50
MAGNABRITE®HS	1.25
Polysorbate 20 (Tween 20)	1.50
Sorbitan Mono-laurate (Span 20)	2.00
Polyvinyl Alcohol	4.00
Sodium Saccharin	0.30
q.s. with water to 100% by volume	

Example 7

<u>Components</u>	
N-acetyl-N-2-octyl-4-iodoaniline	18.00 g
HECTABRITE® DP	1.5 g
Sorbitan Monostearate	0.5 g
Polysorbate 60 (Tween 60)	1.2 g
Poloxamer 338	4.0 g
Sodium Saccharine	0.3 g
Benzoic Acid	0.1 g

- 26 -

Sorbic Acid	0.05 g
Water q.s. to make 100 ml	

Example 8Components

N-(4'-iodophenyl)-2-amino octane	25.00
POLARGEL® NF	2.0 g
Sorbitan Mono-oleate	0.4 g
Polysorbate 20 (Tween 20)	1.2 g
Polvinylalcohol	4.5 g
Sodium Saccharine	0.2 g
Simethicone (food-grade)	0.1 g
Water q.s. to make 100 ml	

Example 9Components

2-Octyl-2,3,5-triiodobenzoate	22.00 g
HECTABRITE®DP	1.50 g
Sorbitan Monostearate	0.70 g
Polysorbate 60 (Tween 60)	1.20 g
Poloxamer 338	4.00 g
Sodium Saccharine	0.30 g
Benzoic Acid	0.50 g
Sorbic Acid	0.05 g
Water q.s. to make 100 ml	

Example 10Components

3,3,4,4,5,5,6,6,7,7,8,8-Dodecafluoro- 2-octyl-2,3,5-triiodobenzoate	22.50 g
POLARGEL®NF	2.30 g
Sorbitan Mono-oleate	0.45 g
Polysorbate 20 (Tween 820)	1.30 g
Polyvinyl Alcohol	4.50 g
Sodium Saccharine	0.25 g

- 27 -

Simethicone emulsion (food-grade)	0.10 g
Water q.s. to make 100 ml	

Example 11Components

Ethyl-3-(2-acetyloxy)-2,4,6-triiodobenzoate	18.50g
MAGNABRITE® HS	1.25 g
Sorbitan monopalmitate	0.60 g
Polyoxyethylene myristyl ether	0.60 g
Polyvinylpyrrolidone	3.50 g
Vanilla flavoring (artificial)	0.25 g
Strawberry flavoring (artificial)	0.25 g
Sorbitol	1.00 g
Water q.s. to make 100 ml	

Example 12Components

2,4,6-Triiodophenoxymethylcyclopentane	22.00 g
HECTABRITE®DP	1.50 g
Sorbitan Monostearate	0.70 g
Polysorbate 60 (Tween 60)	1.20 g
Poloxamer 338	4.00 g
Sodium Saccharine	0.30 g
Benzoic Acid	0.50 g
Sorbic Acid	0.05 g
Water q.s. to make 100 ml	

Example 13Components

2-(4-Iodophenoxy)pentadecane	22.50 g
POLARGEL®NF	2.30 g
Sorbitan Mono-oleate	0.45 g
Polysorbate 20 (Tween 820)	1.30 g

- 28 -

Polyvinyl Alcohol	4.50 g
Sodium Saccharine	0.25 g
Simethicone emulsion (food-grade)	0.10 g
Water q.s. to make 100 ml	

Example 14**Components**

2-Iodophenoxy cyclopentane	18.50 g
MAGNABRITE® HS	1.25 g
Sorbitan monopalmitate	0.60 g
Polyoxyethylene myristyl ether	0.60 g
Polyvinylpyrrolidone	3.50 g
Vanilla flavoring (artificial)	0.25 g
Strawberry flavoring (artificial)	1.25 g
Sorbitol	1.00 g
Water q.s. to make 100 ml	

Example 15**Components**

2,4,6-Triiodophenyl-2-ethylhexanoate	22.00 g
HECTABRITE®DP	1.50 g
Sorbitan Monostearate	0.70 g
Polysorbate 60 (Tween 60)	1.20 g
Poloxamer 338	4.00 g
Sodium Saccharine	0.30 g
Benzoic Acid	0.50 g
Sorbic Acid	0.05 g
Water q.s. to make 100 ml	

Example 16**Components**

2,4,6-Triiodophenyl-tris- (2-ethylhexanoate)	22.50 g
POLARGEL®NF	2.30 g

- 29 -

Sorbitan Mono-oleate	0.45 g
Polysorbate 20 (Tween 820)	1.30 g
Polyvinyl Alcohol	4.50 g
Sodium Saccharine	0.25 g
Simethicone emulsion (food-grade)	0.10 g
Water q.s. to make 100 ml	

Example 17Components

2,4,6-Triiodophenyl hexanesulfonate	18.50 g
MAGNABRITE® HS	1.25 g
Sorbitan monopalmitate	0.60 g
Polyoxyethylene myristyl ether	0.60 g
Polyvinylpyrrolidone	3.50 g
Vanilla flavoring (artificial)	0.25 g
Strawberry flavoring (artificial)	0.25 g
Sorbitol	1.00 g
Water q.s. to make 100 ml	

Example 18Components

Ethyl 3,5-bis(acetylamino)-2,4,6-triiodobenzoate	22.00 g
HECTABRITE®DP	1.50 g
Sorbitan Monostearate	0.70 g
Polysorbate 60 (Tween 60)	1.20 g
Poloxamer 338	4.00 g
Sodium Saccharine	0.30 g
Benzoic Acid	0.50 g
Sorbic Acid	0.05 g
Water q.s. to make 100 ml	

- 30 -

Example 19Components

Ethyl (3,5-bis(acetylamino)-2,4,6-triiodobenzoyloxy) acetate	22.50 g
POLARGEL®NF	2.30 g
Sorbitan Mono-oleate	0.45 g
Polysorbate 20 (Tween 820)	1.30 g
Polyvinyl Alcohol	4.50 g
Sodium Saccharine	0.25 g
Simethicone emulsion (food-grade)	0.10 g
Water q.s. to make 100 ml	

Example 20Components

Ethyl 2-(3,5-bis(acetylamino)-2,4,6-triiodobenzoyloxy) butyrate	18.50 g
MAGNABRITE® HS	1.25 g
Sorbitan monopalmitate	0.60 g
Polyoxyethylene myristyl ether	0.60 g
Polyvinylpyrrolidone	3.50 g
Vanilla flavoring (artificial)	0.25 g
Strawberry flavoring (artificial)	0.25 g
Sorbitol	1.00 g
Water q.s. to make 100 ml	

The surface active agents used in the present invention may be cationic, anionic, nonionic or zwitterionic.

Suitable cationic surfactants include cetyl trimethyl ammonium bromide, cetyl pyridinium chloride, myristyl gamma picolinium chloride and benzalkonium chloride. Suitable anionic agents include sodium lauryl sulphate, sodium heptadecyl sulphate, alkyl benzenesulphonic acids and salts thereof, sodium

- 31 -

butylnapthalene sulfonate, and sulphosuccinates. Zwitterionic surface active agents are substances that when dissolved in water they behave as diprotic acids and, as they ionize, they behave both as a weak base and a weak acid. Since the two charges on the molecule balance each other out they act as neutral molecules. The pH at which the zwitterion concentration is maximum is known as the isoelectric point. Compounds, such as certain amino acids having an isoelectric point at the desired pH of the formulations of the present invention are useful in practicing the present invention.

In preparing the formulations of the present invention we prefer to use nonionic emulsifiers or surface active agents which, similarly to the nonionic contrast agents, possess a superior toxicological profile to that of anionic, cationic or zwitterionic agents. In the nonionic emulsifying agents the proportions of hydrophilic and hydrophobic groups are about evenly balanced. They differ from anionic and cationic surfactants by the absence of charge on the molecule and, for that reason, are generally less irritating than the cationic or anionic surfactants. Nonionic surfactants include carboxylic esters, carboxylic amides, ethoxylated alkylphenols, ethoxylated aliphatic alcohols, ethylene oxide polymer or ethylene oxide/propylene oxide co-polymers polyvinylpyrrolidone and polyvinylalcohol.

One particular type of carboxylic ester nonionic surface active agents are the partial, for example mono-, esters formed by the reaction of fatty and resin acids, for example of about 8 to about 18 carbon atoms, with polyalcohols, for example glycerol, glycols such as mono-, di-, tetra- and hexaethylene glycol, sorbitan, and the like; and similar compounds formed by the direct addition of varying molar ratios of ethylene oxide to the hydroxy group of fatty acids.

- 32 -

Another type of carboxylic esters are the condensation products of fatty and resin partial acids, for example mono-, esters ethylene oxide, such as fatty or resin acid esters of polyoxyethylene sorbitan and sorbitol, for example polyoxyethylene sorbitan, mono-tall oil esters. These may contain, for example, from about 3 to about 80 oxyethylene units per molecule and fatty or resin acid groups of from about 8 to about 18 carbon atoms. Examples of naturally occurring fatty acid mixtures which may be used are those from coconut oil and tallow while examples of single fatty acids are dodecanoic acid and oleic acid.

Carboxylic amide nonionic surface active agents are the ammonia, monoethylamine and diethylamine amides of fatty acids having an acyl chain of from about 8 to about 18 carbon atoms.

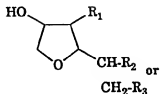
The ethoxylated alkylphenol nonionic surface active agents include various polyethylene oxide condensates of alkylphenols, especially the condensation products of mono-alkylphenols or dialkylphenols wherein the alkyl group contains about 6 to about 12 carbon atoms in either branched chain or particularly straight chain configuration, for example, octyl cresol, octyl phenol or nonyl phenol, with ethylene oxide, said ethylene oxide being present in amounts equal to from about 5 to about 25 moles of ethylene oxide per mole of alkylphenol.

Ethoxylated aliphatic alcohol nonionic surface active agents include the condensation products of aliphatic alcohols having from about 8 to 18 carbon atoms in either straight chain or branched chain configuration, for example oleyl or cetyl alcohol, with ethylene oxide, said ethylene oxide being present in equal amounts from about 30 to about 60 moles of ethylene oxide per mole of alcohol.

Preferred nonionic surface active agents include:

- 33 -

(a) Sorbitan esters (sold under the trade name Span) having the formula:



wherein

$R_1 = R_2 = \text{OH}$, $R_3 = \text{R}$ for sorbitan monoesters,

$R_1 = \text{OH}$, $R_2 = R_3 = \text{R}$ for sorbitan diesters,

$R_1 = R_2 = R_3 = \text{R}$ for sorbitan triesters,

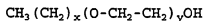
where $\text{R} = (\text{C}_{11}\text{H}_{23})\text{COO}$ for laurate,

$(\text{C}_{17}\text{H}_{33})\text{COO}$ for oleate,

$(\text{C}_{15}\text{H}_{31})\text{COO}$ for palmitate,

$(\text{C}_{17}\text{H}_{35})\text{COO}$ for stearate;

(b) Polyoxyethylene alkyl ethers (i.e. Brij's) having the formula:



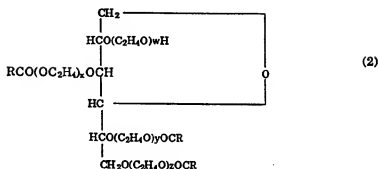
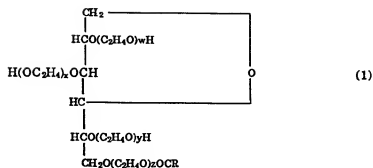
where $(x + 1)$ is the number of carbon atoms in the alkyl chain, typically:

12	lauryl	(dodecyl)
14	myristyl	(tetradecyl)
16	cetyl	(hexadecyl)
18	stearyl	(octadecyl)

and y is the number of ethylene oxide groups in the hydrophilic chain, typically 10-60;

(c) Polyoxyethylene sorbitan fatty acid esters, sold under the trade names of Tween or Polysorbates 20, 40, 60, 65, 80 & 85 having the formulae (1) and (2)

- 34 -



wherein

- $w+x+y+z = 20$ (Polysorbate 20, 40, 60, 65, 80 and 85)
 $w+x+y+z = 5$ (Polysorbate 81)
 $w+x+y+z = 4$ (Polysorbate 21 and 61).

- (d) Polyoxyethylene stearates, such as:
 poly(oxy-1,2-ethanediyl), α -hydro- ω -hydroxy-octadecanoate;
 polyethylene glycol monostearate; and
 poly(oxy-1,2-ethanediyl)- α -(1-oxooctadecyl)- ω -hydroxy-polyethylene glycol monostearate.

- (e) Polyethylene oxide/polypropylene oxide block copolymers, sold under the name PLURONIC™, which include Poloxamer 407 (PLURONIC™ F127), Poloxamer 188 (PLURONIC™ F68), Poloxamer 237 (PLURONIC™ F87) and Poloxamer 338 (PLURONIC™ F108).

- 35 -

(f) Polyvinylpyrrolidone.

(g) Polyvinylalcohol.

The dosages of the contrast agent used according to the method of the present invention will vary according to the precise nature of the contrast agent used. Preferably, however, the dosage should be kept as low as is consistent with achieving contrast enhanced imaging. By employing as small amount of contrast agent as possible, toxicity potential is minimized. For most contrast agents of the present invention dosages will be in the range of from about 0.1 to about 16.0 g iodine/kg body weight, preferably in the range of from about 0.5 to about 6.0 g iodine/kg of body weight, and most preferably, in the range of from about 1.2 to about 2.0 g iodine/kg body weight for regular x-ray visualization of the GI tract. For CT scanning the contrast agents of the present invention will be in the range of from about 1 to about 600 mg iodine/kg body weight, preferably in the range of from about 20 to about 200 mg iodine/kg body weight, and most preferably in the range of from about 40 to about 80 mg iodine/kg body weight.

When administered to mammals, the compositions of the present invention produce excellent x-ray and CT images.

- 36 -

CLAIMS:

1. An x-ray contrast composition for oral or retrograde examination of the gastrointestinal tract comprising on a % weight per volume basis:

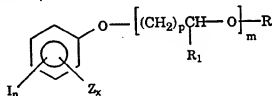
(a) a contrast agent selected from (1) from about 5 to 45% of an x-ray contrast producing agent having the formula



or a pharmaceutically acceptable salt thereof wherein


R is a substituted or unsubstituted alkyl group containing from 2 to 8 carbon atoms, wherein said substituents are selected from the group consisting of C₁-C₆ alkyl, hydroxy and alkoxy; and n is 1 to 5; or

(2) from about 5 to 45% of an x-ray contrast producing agent having the formula,



or a pharmaceutically acceptable salt thereof wherein

Z is H, halo, C₁-C₂₀ alkyl, cycloalkyl, lower alkoxy, alkoxy carbonyl, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C₁-C₂₅ alkyl, cycloalkyl,  or halo-lower-alkyl, each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy; or (CR₁R₂)_p-(CR₃=CR₄)_mQ, or (CR₁R₂)_p-C=C-Q;

- 37 -

R_1 , R_2 , R_3 and R_4 are independently H or lower-alkyl, optionally substituted with halo;

x is 1-4;

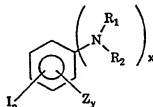
n is 1-4;

m is 1-15;

p is 1-20; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower alkyl;

(3) from about 5 to 45% of an x-ray contrast producing agent having the formula,



or a pharmaceutically acceptable salt thereof wherein

Z is H, halo, C_1 - C_{20} alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R_1 and R_2 are independently H, C_1 - C_{25} alkyl, cycloalkyl, acetyl or halo-lower-alkyl, wherein said C_1 - C_{25} alkyl, cycloalkyl and halo lower-alkyl are optionally substituted with fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy and said acetyl is optionally substituted with fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy;

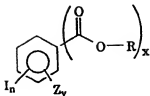
n is 1-4;

y is 1-4; and

x is 1 or 2;

(4) from about 5 to 45% of an x-ray contrast producing agent having the formula

- 38 -



or a pharmaceutically acceptable salt thereof wherein

Z is H, halo, C₁-C₂₀ alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C₁-C₂₅ alkyl, cycloalkyl, or halo-lower-alkyl, each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy; or (CR₁R₂)_p-(CR₃=CR₄)_mQ, or (CR₁R₂)_p-C≡C-Q;

R₁, R₂, R₃ and R₄ are independently lower-alkyl, optionally substituted with halo;

x is 1-3

y is 1-4;

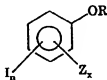
n is 1-5;

m is 1-15;

p is 1-10; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower alkyl;

(5) from about 5 to 45% of an x-ray contrast producing agent having the formula,



or a pharmaceutically acceptable salt thereof wherein

Z is H, halo, C₁-C₂₀ alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is methyl, ethyl, propyl, C₉-C₂₅ alkyl, cycloalkyl, or halo-lower-alkyl, optionally substituted

- 39 -

with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy; or $(CR_1R_2)_p - (CR_3=CR_4)_mQ$, or $(CR_1R_2)_p - C \equiv C - Q$;

R_1 , R_2 , R_3 and R_4 are independently lower-alkyl, optionally substituted with halo;

x is 1-4;

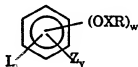
n is 1-5;

m is 1-15;

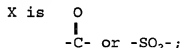
p is 1-10; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower alkyl;

(6) from about 5 to 45% of an x-ray contrast producing agent having the formula,



or a pharmaceutically acceptable salt thereof wherein



Z is H, halo, methyl, ethyl, n-propyl, C_4 - C_{20} alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C_1 - C_{25} alkyl, cycloalkyl or aryl each of which may be optionally substituted with halo, fluoro-lower-alkyl, lower-alkoxy, hydroxy, carboxy or lower-alkoxy carbonyl; lower-alkenyl, lower-alkynyl, lower-alkylene or lower-alkoxy-carbonyloxy;

n is 1-5;

y is 0-4; and

w is 1-4;

- 40 -

(7) from about 5 to 45% of a crystalline contrast producing agent selected from the group consisting of diatrizoic acid, metrizoic acid, iothalamic acid, trimesic acid, urokonic acid, ioxathalamic acid, tetraiodoterephthalic acid, ioxaglic acid, iodipamide, ethyl-3,5-diacetamido-2,4,6-triiodobenzoate, ethyl-2-(3,5-bis(acetylamino)-2,4,6-triiodo-benzoyloxy)butyrate, and ethyl(3,5-bis(acetylamino)-2,4,6-triiodobenzoyloxy)-acetate, said crystalline contrast agent having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of from about 0.5 μ to about 100 μ ; and said surface modifier is selected from the group consisting of tetrafunctional block copolymers derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine;

- (b) from about 0.1 to 10% of a pharmaceutically acceptable clay selected from the group consisting of: montmorillonite, beidelite, nontronite, hectorite and saponite;
- (c) from about 1.0 to 20% of a surfactant selected from the group consisting of nonionic, anionic, cationic and zwitterionic surfactants;
- (d) from about 0 to 15% of an excipient; and
- (e) water to make 100% by volume.

2. The x-ray contrast composition of claim 1 wherein said x-ray contrast producing agent is present in an amount of from about 10 to 35%.

3. The x-ray contrast composition of claim 1 wherein said pharmaceutically acceptable clay constitutes from 0.5 to 5% of the composition.

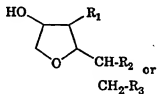
- 41 -

4. The x-ray contrast composition of claim 1 wherein said surfactant constitutes from 2 to 10% of the composition.

5. The x-ray contrast composition of claim 1 wherein said excipient constitutes from 0.5 to 5% of the composition.

6. The x-ray contrast composition of claim 1 wherein said nonionic surface active agent is selected from the group consisting of carboxylic esters, carboxylic amides, ethoxylated alkylphenols, ethoxylated aliphatic alcohols, ethylene oxide polymer, ethylene oxide/propylene oxide co-polymer, polyvinylpyrrolidone and polyvinylalcohol.

7. The x-ray contrast composition of claim 1 wherein said surfactant is sorbitan ester having the formula:



wherein

$\text{R}_1 = \text{R}_2 = \text{OH}$, $\text{R}_3 = \text{R}$ for sorbitan monoesters,

$\text{R}_1 = \text{OH}$, $\text{R}_2 = \text{R}_3 = \text{R}$ for sorbitan diesters,

$\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{R}$ for sorbitan triesters,

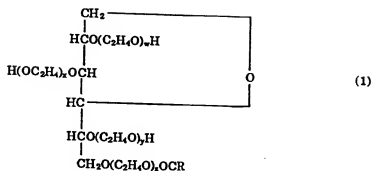
where $\text{R} = (\text{C}_{11}\text{H}_{23})\text{COO}$ for laurate,
 $(\text{C}_{17}\text{H}_{33})\text{COO}$ for oleate,
 $(\text{C}_{15}\text{H}_{31})\text{COO}$ for palmitate or
 $(\text{C}_{17}\text{H}_{35})\text{COO}$ for stearate.

8. The x-ray contrast composition of claim 1 wherein said surface active agent is polyoxyethylene stearate.

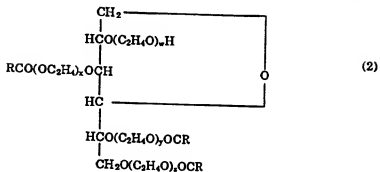
9. The x-ray contrast composition of claim 1 wherein said surfactant is polyoxyethylene sorbitan fatty acid

- 42 -

ester of the formulae (1) and (2)



Polyoxyethylene sorbitan monoester



wherein

$$w+x+y+z = 20$$

$$w+x+y+z = 5$$

$$w+x+y+z = 4.$$

10. A method of carrying out x-ray examination of the gastrointestinal tract of a patient, said method comprises the oral or rectal administration to the patient an x-ray contrast formulation of any preceding claim.

INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/GB 95/00566

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K49/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	US, A, 5 360 604 (STEPHEN B. RUDDY) 1 November 1994 see the whole document ---	1-10
X	GB, A, 767 788 (SCHERING CO.) 6 February 1957 see page 5, column 1, line 27 - line 31; claims ---	1
X	CH, A, 338 274 (SCHERING CO.) 30 June 1959 see page 2, column 1, line 17 - line 17; claims ---	1
A	FR, A, 2 085 692 (E. R. SQUIBB & SONS, INC.) 31 December 1971 see claims 1-3; example 3 --- -/-	1

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

29 June 1995

Date of mailing of the international search report

25. 07. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

BERTE, M

INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/GB 95/00566

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 568 155 (STERLING WINTHROP INC) 3 November 1993 cited in the application see page 6, column 48 - column 58; claims see page 6, column 14 - column 15 see page 7, line 39 - page 8, line 14 ---	1-10
A	EP,A,0 568 156 (STERLING WINTHROP INC) 3 November 1993 see page 3, line 55 - page 5, line 34; claims ---	1-10
P,A	EP,A,0 603 922 (STERLING WINTHROP INC) 29 June 1994 see page 6, line 45 - line 48; claims ---	1-10
P,A	EP,A,0 603 923 (STERLING WINTHROP INC) 29 June 1994 see claims ---	1-10
P,A	EP,A,0 609 589 (STERLING WINTHROP INC) 10 August 1994 see claims ---	1-10
P,A	EP,A,0 614 668 (STERLING WINTHROP INC) 14 September 1994 see page 5, line 28 - page 7, line 29 ---	1-10
P,A	US,A,5 316 755 (ILLIG CARL R ET AL) 31 May 1994 see column 27, line 17 - column 29, line 55; claims ---	1-10
P,A	US,A,5 308 607 (JOSEF KURT A ET AL) 3 May 1994 see column 13, line 47 - column 16, line 9; claims ---	1-10
P,A	US,A,5 310 537 (ILLIG CARL R. ET AL.) 10 May 1994 see column 5, line 51 - column 8, line 18; claims & EP,A,0 613 690 ---	1-10
P,A	US,A,5 310 538 (BACON EDWARD R ET AL) 10 May 1994 cited in the application see column 12, line 65 - column 17, line 4; claims & EP,A,0 614 670 ---	1-10

-/--

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 95/00566

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	US,A,5 312 616 (ILLIG CARL R ET AL) 17 May 1994 cited in the application see column 10, line 50 - column 15, line 35; claims & EP,A,0 614 669 ---	1-10
P,A	US,A,5 336 484 (BACON EDWARD R ET AL) 9 August 1994 cited in the application see column 13, line 10 - column 17, line 55; claims & EP,A,0 617 970 ---	1-10
P,A	US,A,5 318 769 (BACON EDWARD R ET AL) 7 June 1994 see column 12, line 1 - column 14, line 35; claims ---	1-10
P,A	US,A,5 326 553 (ILLIG CARL R ET AL) 5 July 1994 cited in the application see column 27, line 17 - column 31, line 59; claims & EP,A,0 609 587 -----	1-10

INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/GB 95/00566

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5360604	01-11-94	US-A- 5368837	29-11-94
GB-A-767788		NONE	
CH-A-338274		NONE	
FR-A-2085692	31-12-71	CA-A- 985626 CH-A- 535050 DE-A- 2110932 GB-A- 1353635 US-A- 3984571	16-03-76 31-03-73 23-09-71 22-05-74 05-10-76
EP-A-0568155	03-11-93	AU-B- 3831593 HU-A- 64700 JP-A- 6025016 US-A- 5318768 US-A- 5342605 US-A- 5352434 US-A- 5405600	04-11-93 28-02-94 01-02-94 07-06-94 30-08-94 04-10-94 11-04-95
EP-A-0568156	03-11-93	US-A- 5260049 AU-B- 3831693 HU-A- 65306 JP-A- 6025017	09-11-93 04-11-93 02-05-94 01-02-94
EP-A-0603922	29-06-94	US-A- 5322679 AU-B- 4737593 CA-A- 2106413 CZ-A- 9302748 FI-A- 935308 HU-A- 65772 JP-A- 6199754 NO-A- 934333	21-06-94 30-06-94 17-06-94 13-07-94 17-06-94 28-07-94 19-07-94 17-06-94
EP-A-0603923	29-06-94	AU-B- 5046793 CA-A- 2102269 FI-A- 935307 HU-A- 66332 JP-A- 6228068 NO-A- 934316	23-06-94 15-06-94 15-06-94 28-11-94 16-08-94 15-06-94

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 95/00566

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0603923		US-A- 5384107	24-01-95
EP-A-0609589	10-08-94	US-A- 5334370 AU-B- 5047093 CA-A- 2109443 CZ-A- 9400110 FI-A- 940007 JP-A- 6234664 NO-A- 934770	02-08-94 11-08-94 05-08-94 17-08-94 05-08-94 23-08-94 05-08-94
EP-A-0614668	14-09-94	US-A- 5344638 AU-B- 5768194 CA-A- 2116832 HU-A- 66946 JP-A- 6321867	06-09-94 15-09-94 12-09-94 30-01-95 22-11-94
US-A-5316755	31-05-94	AU-B- 4622593 CA-A- 2105729 CZ-A- 9400140 EP-A- 0609586 FI-A- 940006 HU-A- 67315 JP-A- 6234687 NO-A- 934794	04-08-94 03-08-94 17-08-94 10-08-94 03-08-94 28-03-95 23-08-94 03-08-94
US-A-5308607	03-05-94	AU-B- 5046993 CA-A- 2102247 CZ-A- 9400109 EP-A- 0609588 FI-A- 940008 JP-A- 6234673 NO-A- 934795 NZ-A- 250064 US-A- 5385721	11-08-94 05-08-94 17-08-94 10-08-94 05-08-94 23-08-94 05-08-94 25-11-94 31-01-95
US-A-5310537	10-05-94	AU-B- 5644694 CA-A- 2114903 EP-A- 0613690 HU-A- 68191 JP-A- 6298710	08-09-94 02-09-94 07-09-94 29-05-95 25-10-94

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 95/00566

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
EP-A-0613690	07-09-94	US-A-	5310537	10-05-94
		AU-B-	5644694	08-09-94
		CA-A-	2114903	02-09-94
		HU-A-	68191	29-05-95
		JP-A-	6298710	25-10-94

US-A-5310538	10-05-94	AU-B-	5767994	15-09-94
		CA-A-	2115794	12-09-94
		EP-A-	0614670	14-09-94
		HU-A-	68143	29-05-95
		JP-A-	6321814	22-11-94

EP-A-0614670	14-09-94	US-A-	5310538	10-05-94
		AU-B-	5767994	15-09-94
		CA-A-	2115794	12-09-94
		HU-A-	68143	29-05-95
		JP-A-	6321814	22-11-94

US-A-5312616	17-05-94	AU-B-	5768294	15-09-94
		CA-A-	2116831	12-09-94
		EP-A-	0614669	14-09-94
		JP-A-	6321813	22-11-94
		US-A-	5385720	31-01-95

EP-A-0614669	14-09-94	US-A-	5312616	17-05-94
		AU-B-	5768294	15-09-94
		CA-A-	2116831	12-09-94
		JP-A-	6321813	22-11-94
		US-A-	5385720	31-01-95

US-A-5336484	09-08-94	AU-B-	5914694	06-10-94
		CA-A-	2115907	01-10-94
		EP-A-	0617970	05-10-94
		HU-A-	66557	28-12-94
		JP-A-	6321815	22-11-94

EP-A-0617970	05-10-94	US-A-	5336484	09-08-94
		AU-B-	5914694	06-10-94
		CA-A-	2115907	01-10-94

INTERNATIONAL SEARCH REPORT

 Intern al Application No
 PCT/GB 95/00566

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0617970		HU-A- 66557 JP-A- 6321815 US-A- 5372800	28-12-94 22-11-94 13-12-94
US-A-5318769	07-06-94	AU-B- 5914794 CA-A- 2115910 EP-A- 0617969 JP-A- 6321865 US-A- 5385722	06-10-94 01-10-94 05-10-94 22-11-94 31-01-95
US-A-5326553	05-07-94	AU-B- 4616193 CA-A- 2105730 CZ-A- 9400171 EP-A- 0609587 FI-A- 940005 HU-A- 67347 JP-A- 6234663 NO-A- 934793	04-08-94 03-08-94 17-08-94 10-08-94 03-08-94 28-03-95 23-08-94 03-08-94
EP-A-0609587	10-08-94	US-A- 5326553 AU-B- 4616193 CA-A- 2105730 CZ-A- 9400171 FI-A- 940005 HU-A- 67347 JP-A- 6234663 NO-A- 934793	05-07-94 04-08-94 03-08-94 17-08-94 03-08-94 28-03-95 23-08-94 03-08-94

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB95/00566

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 10 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-2, 4
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
please see enclosure!
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/J210

Meaningful search not possible....

II.) Obscurities,...

In view of the definition of products by means of their biological, chemical, and/or pharmacological properties, the search has to be restricted for economic reasons.

The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims or examples. (see guidelines Part B, Chapter III, paragraph 3.6)